UNITED STATES PATENT AND TRADEMARK OFFICE

UNITED STATES DEPARTMENT OF COMMERCE
United States Patent and Trademark Office
Address: COMMISSIONER FOR PATENTS
P.O. Box 1450
Alexandria, Virginia 22313-1450
www.uspto.gov

APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/998,833	11/30/2001	Philip E. Thorpe	4001.002299/UTSD:0549-2	8102

52101 7590 10/20/2005

PEREGRINE PHARMACEUTICALS, INC.
5353 WEST ALABAMA
SUITE 306
HOUSTON, TX 77056

EXAMINER	
FETTEROLF, BRANDON J	

ART UNIT	PAPER NUMBER
1642	

DATE MAILED: 10/20/2005

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/998,833	THORPE ET AL.	
	Examiner	Art Unit	
	Brandon J. Fetterolf, PhD	1642	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *01 July 2005*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *4-9,23-27,41 and 49-83* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *4-9, 23-27, 41 and 49-83* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

2

Response to the Amendment

The Amendment filed on 07/01/2005 in response to the previous Non-Final Office Action (03/28/2005) is acknowledged and has been entered.

The Examiner apologizes for the error made in the second Action listing claims 4-9, 23-27 and 4-42 as pending and thanks Applicant's for pointing this out.

Claims 4-9, 23-27, 41 and 49-83 are currently pending and under consideration.

The text of those sections of Title 35, U.S. Code not included in this action can be found in a prior Office Action.

Rejections Withdrawn:

The rejection of claims 4, 6-7, 9, 25, 41, 49-50, 57-58, 61, 64-65, 67-68, 71, 73, 75-78 and 80-82 under 35 U.S.C. 103(a) as being unpatentable over Schoit (IDS, U.S. 6,300,308, 12/31/1997) in combination with Hudziak *et al.* (U.S. 5,725,856, 1998) has been withdrawn in view of the Statement of Common Ownership (Remarks, Page 28).

Rejections Maintained:

Claims 4-9, 24, 27, 41, and 49-82 **remain** rejected and **new** claim 83 is rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 1-11, 17-20, 27-54 of U.S. Patent No. 6,783,760 for the reasons of record in the prior Action (3/28/2005, pages 2-3) and for the reasons set forth below.

In reference to the prior office action which held that although the conflicting claims are not identical, they are not patentably distinct from each other because the method of treating an animal having a vascularized tumor with at least an agent that binds to an aminophospholipid and at least a second anti-tumor agent, wherein the agent is an antibody claimed in the patent appears to fall within the same scope of the method of treating an animal having a vascularized tumor with at least an antibody that binds to an aminophosholipid and at least a second therapeutic agent claimed in

the application being examined, Applicant's contend that the '760 patent claims methods for treating vascularized tumors by administering at least a first binding ligand that comprises at least a first therapeutic agent operatively attached to a targeting agent that binds to an aminophospholipid, in combination with surgery, radiotherapy or at least a second anti-cancer agent. Specifically, Applicants point out that the '760 patent requires the administration of a therapeutic conjugate, e.g., a therapeutic agent is delivered to the tumor by attachment to a targeting agent that binds to an aminopohospholipid, which is in contrast to the combination therapy claims of the present application that rely on the administration of a naked or unconjugated antibody.

These arguments have been carefully considered, but are not found persuasive.

First, the previous rejection was based on the technical reasoning that a patent to a method of treating an animal having a vascularized tumor with at least an antibody that binds to an aminophosholipid and at least a second therapeutic agent would necessarily, extend the rights of a method of treating an animal having a vascularized tumor with at least an agent such as an antibody that binds to an aminophospholipid and at least a second anti-tumor agent should the application being examined issue as a patent after the conflicting patent. In the instant case, the Examiner agrees with Applicants contention that the currently pending claims do not specifically recite that the antibody is conjugated to a therapeutic agent. However, the currently pending claims do not appear to exclude a conjugate, nor do the currently pending claims appear to recite the limitation that the antibody is naked or unconjugated. Thus, it appears that Applicants are arguing limitations that are not present in the currently pending claims. Therefore, claims 4-9, 24, 27, 41, and 49-82 remain rejected and new claim 83 is rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 1-11, 17-20, 27-54 of U.S. Patent No. 6,783,760.

Claims 4-9, 41, 49-51, 53, 57-58, 61, 68-71, 75-78 and 80-82 **remain** rejected and **new** claim 83 is rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 4-11, 28-29 and 43 of U.S. Patent No. 6,312,694 for the reasons of record in the prior Action (3/28/2005, page 3) and for the reasons set forth below

In reference to the prior office action which held that although the conflicting claims are not identical, they are not patentably distinct from each other because the method of treating an animal having a vascularized tumor with at least an agent that binds to an aminophospholipid and at least a

second anti-tumor agent, wherein the agent is an antibody claimed in the patent appears to fall within the same scope of the method of treating an animal having a vascularized tumor with at least an antibody that binds to an aminophosholipid and at least a second therapeutic agent claimed in the application being examined, Applicant's reiterate (remarks, page 21) the arguments as discussed above for the '760 patent claims in a continuation of the '694 patent. Specifically, Applicants point out that the '694 patent is also limited to a therapeutic conjugate, which is in contrast to the combination therapy claims of the present application that rely on the administration of a naked or unconjugated antibody.

These arguments have been carefully considered, but are not found persuasive.

First, the previous rejection was based on the technical reasoning that a patent to a method of treating an animal having a vascularized tumor with at least an antibody that binds to an aminophosholipid and at least a second therapeutic agent would necessarily, extend the rights of a method of treating an animal having a vascularized tumor with at least an agent such as an antibody that binds to an aminophospholipid and at least a second anti-tumor agent should the application being examined issue as a patent after the conflicting patent. In the instant case, the Examiner agrees with Applicants contention that the currently pending claims do not specifically recite that the antibody is conjugated to a therapeutic agent. However, the currently pending claims do not appear to exclude a conjugate, nor do the currently pending claims appear to recite the limitation that the antibody is naked or unconjugated. Thus, it appears that Applicants are arguing limitations that are not present in the currently pending claims. Therefore, claims 4-9, 41, 49-51, 53, 57-58, 61, 68-71, 75-78 and 80-82 remain rejected and new claim 83 is rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 4-11, 28-29 and 43 of U.S. Patent No. 6,312,694.

New Rejections:

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or

with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 4-9, 23-27, 41 and 49-83 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

The factors to be considered in determining the written description requirement include:

1. A determination as to what the claim as a whole covers.
   The examiner should consider and discuss the full scope of the claim.
2. A full review of the application to understand how applicant provides support for the claimed invention including each element and/or step.
   This requirement includes comparing the claim scope with the scope of the description.
3. A determination as to whether the applicant was in possession of the claimed invention as a whole at the time of filing.
   This should include the following considerations:
   a. Actual reduction to practice
   b. Disclosure of drawings or structural chemical formulas
   c. Sufficient relevant identifying characteristics
      i. Complete structure
      ii. Partial structure
      iii. Physical and/or chemical properties
      iv. Functional characteristics when coupled with a known or disclosed correlation between function and structure
   d. Method of making the claimed invention
   e. Level of skill and knowledge in the art
   f. Predictability in the art
4. For each claim drawn to a single embodiment or species, consider the above factors in regard to that embodiment or species to determine whether one skilled in the art would recognize that applicant was in possession of the species or embodiment at the time of filing.
5. For each claim drawn to a genus, consider each of the above factors to determine whether there is disclosure of a representative number of species which would lead one skilled in the art to conclude that applicant was in possession of the claimed invention. The number of species required to represent a genus will vary inversely with the level of skill and knowledge in the art and the variability among the claimed genus.

In the instant case, the claims are inclusive of a method of treating an animal having a vascularized tumor, comprising simultaneously or sequentially administering a therapeutically effective combination of at least a first pharmaceutical composition comprising at least a first

antibody, or antigen-binding fragment thereof, that binds to an aminophospholipid on the luminal surface of blood vessels of the vascularized tumor and at least a second therapeutic agent; wherein the second therapeutic agent is: a chemotherapeutic agent, an anti-angiogenic agent, an inflammatory cytokine, H_2O_2, thrombin, a compound that interferes with tubulin activity or a calcium flux inducing agent. Thus, the claims are inclusive of a genus of second therapeutic agents further characterized by 5 subgenera and two specific agents.

The specification teaches (page 33, lines 5-20) that specific therapeutic agents of the invention include, but are not limited to, anti-cancer agents which are designed to increase aminophospholipid expression by injuring or inducing apoptosis in the tumor endothelium such as chemotherapeutic agents, anti-angiogenic agents, cytokines, and calcium-flux agents. With regards to the chemotherapeutic agent, the specification (pages 124 to 126, Table B) provides a list of chemotherapeutic agents, which have been found to be useful in treating neoplastic diseases. With regards to the anti-angiogenic agent, the specification (pages 128-129, Table C) discloses a list of inhibitors and/or negative regulators of angiogenesis. With regards to the cytokines, the specification (page 121, lines 16-23 and Preliminary amendment, 11/30/2001, page 15) teaches that cytokines which may be employed in the combination approach include not only interleukin 4, but also Il-1α, IL-1β, IL-2, IL-3, ... IFN-α, IFN-β and IFN-γ. With regards to the calcium-flux agent, the specification teaches (Preliminary amendment, 11/30/2001, page 15) that a rise in intracellular $Ca2^+$ might activate scramblase and simultaneously inhibits aminophospholipid translocase which leads to an accumulation of PS on the external side of the membrane. Thus, while the specification contemplates a mechanism by which a calcium-flux agent may be used, the specification does not reasonably convey to those of skill in the art that applicants were in possession of the claimed genus of calcium-flux agents. A description of a genus may be achieved by means of a recitation of a representative number of species falling within the scope of the genus or by describing structural features common the genus that "constitute a substantial portion of the genus." See University of California v. Eli Lilly and Co., 119 F.3d 1559, 1568, 43 USPQ2d 1398, 1406 (Fed. Cir. 1997): "A description of a genus of cDNAs may be achieved by means of a recitation of a representative number of cNDA, defined by nucleotide sequence, falling within the scope of the genus or of a recitation of structural features common to the members of the genus, which features constitute a substantial portion of the genus."

The court has since clarified that this standard applies to compounds other than cDNAs. See University of Rochester v. G.D. Searle & Co., Inc., __F.3d__,2004 WL 260813, at *9 (Fed.Cir.Feb. 13, 2004). The instant specification fails to provide sufficient descriptive information, such as definitive structural or functional features that are common to the genus. That is, the specification provides neither a representative number of calcium flux inducing agents that encompass the genus nor does it provide a description of structural features that are common to the calcium flux inducing agents. Since the disclosure fails to describe the common attributes or characteristics that identify members of the genus, and because the genus is highly variant, the disclosure is insufficient to describe the genus. Thus, one of skill in the art would reasonably conclude that the disclosure fails to provide a representative number of species to describe and enable the genus as broadly claimed.

Vas-Cath Inc. v. Mahurkar, 19USPQ2d 1111, clearly states "applicant must convey with reasonable clarity to those skilled in the art that, as of the filing date sought, he or she was in possession *of the invention*. The invention is, for purposes of the 'written description' inquiry, *whatever is now claimed*." (See page 1117.) The specification does not "clearly allow persons of ordinary skill in the art to recognize that [he or she] invented what is claimed." (See *Vas-Cath* at page 1116). As discussed above, the skilled artisan cannot envision the detailed chemical structure(s) of the encompassed genus of calcium flux inducing agents, and therefore conception is not achieved until reduction to practice has occurred, regardless of the complexity or simplicity of the method of isolation. Adequate written description requires more than a mere statement that it is part of the invention and reference to a potential method of isolating it. The compound itself is required. See *Fiers v. Revel*, 25 USPQ2d 1601 at 1606 (CAFC 1993) and *Amgen Inc. v. Chugai Pharmaceutical Co. Ltd.*, 18 USPQ2d 1016.

One cannot describe what one has not conceived. See *Fiddes v. Baird*, 30 USPQ2d 1481 at 1483. In *Fiddes*, claims directed to mammalian FGF's were found to be unpatentable due to lack of written description for that broad class. The specification provided only the bovine sequence.

Applicant is reminded that *Vas-Cath* makes clear that the written description provision of 35 U.S.C. §112 is severable from its enablement provision (see page 1115).

Claims 4-5 and 7-9, 23-27, 41 and 49-83 rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for a method of treating an animal having a

vascularized tumor, comprising simultaneously or sequentially administering an animal a therapeutically effective combination of at least a first pharmaceutical composition comprising a first antibody, or antigen-binding fragment thereof that binds to phosphatidylserine on the luminal surface of blood vessels of the vascularized tumor and a second therapeutic agent, wherein the second therapeutic agent is a chemotherapeutic agent, anti-angiogenic agent, an inflammatory cytokine or a compound that interferes with tubulin activity, does not reasonably provide enablement for a method of treating an animal having a vascularized tumor, comprising simultaneously or sequentially administering to an animal a therapeutically effective combination of at least a first pharmaceutical composition comprising a first antibody, or antigen-binding fragment thereof that binds to any and/or all aminophospholipids on the luminal surface of blood vessels of the vascularized tumor and a second therapeutic agent, wherein the second therapeutic agent is H2O2, thrombin, or a calcium flux inducing agent. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to use the invention commensurate in scope with these claims.

The factors to be considered in determining whether undue experimentation is required are summarized In re Wands 858 F.2d 731, 8 USPQ2nd 1400 (Fed. Cir, 1988). The court in Wands states: "Enablement is not precluded by the necessity for some experimentation such as routine screening. However, experimentation needed to practice the invention must not be undue experimentation. The key word is 'undue,' not 'experimentation.' " (Wands, 8 USPQ2d 1404). Clearly, enablement of a claimed invention cannot be predicated on the basis of quantity of experimentation required to make or use the invention. "Whether undue experimentation is needed is not a single, simple factual determination, but rather is a conclusion reached by weighing many factual considerations." (Wands, 8 USPQ2d 1404). The factors to be considered in determining whether undue experimentation is required include: (1) the quantity of experimentation necessary, (2) the amount or direction or guidance presented, (3) the presence or absence of working examples, (4) the nature of the invention, (5) the state of the prior art, (6) the relative skill of those in the art, (7) the predictability or unpredictability of the art, and (8) the breadth of the claims.

The instant claims read on a method of treating an animal having a vascularized tumor, comprising simultaneously or sequentially administering to an animal a therapeutically effective combination of at least a first pharmaceutical composition comprising a first antibody, or antigen-

binding fragment thereof that binds to an aminophospholipid on the luminal surface of blood vessels of the vascularized tumor and a second therapeutic agent. Thus, the claims read on method of treating a vascularized tumor comprising administering an antibody that binds to any and/or all aminophospholipid on the luminal surface of blood vessels of a vascularized tumor.

The scope of the instant claims is not commensurate with the enablement of the instant disclosure, because practice of the claimed invention would require undue experimentation by an artisan of ordinary skill in the art. The instant specification is not enabling for claims drawn to treating an animal having a vascularized tumor, comprising simultaneously or sequentially administering to an animal a therapeutically effective combination of at least a first pharmaceutical composition comprising a first antibody, or antigen-binding fragment thereof that binds to any and/or all aminophospholipids on the luminal surface of blood vessels of the vascularized tumor and a second therapeutic agent. The specification (page 6, line 27 to page 7, line 4) teaches that the preferred amino phospholipids of the invention include, but are not limited to, negatively charged phosphatydilserine ("PS"), neutral zwitterionic phosphatidylethanolamine ("PE") and any other aminophospholipid target which is expressed, accessible or complexed on the luminal surface of tumor vascular endothelial cells. Moreover, the specification discloses a variety of examples showing phosphatydilserine expression in tumor blood vessels, externalized phosphatydilserine as a global marker for tumor blood vessels and the in vivo anti-tumor effects of unconjugated anti-phosphatydilserine antibodies administered to tumor bearing mice (Examples VIII page 163, XI page 167and XII page 170). The specification further provides studies with cultured endotherlial cells that showed hypoxia/reoxygeneration, acidity, thrombin, inflammatory cytokines and hydrogen peroxide caused PS exposure without causing cytotoxicity (Preliminary amendment, 11/30/2001, page 5). Although the specification teaches that anti-PS which binds to the aminophospholipid phosphatydilserine on the luminal surface of blood vessels of a vascularized tumor can be used in a method of treating a vascularized tumor, the specification appears to be silent on a correlation between the use of any antibody to any and/or all aminophospholipid and the treatment of a vascularized tumor; and further, the specification does not appear to suggest a nexus between the expression, accessibility and/or complexation of any other aminophospholipid on the luminal surface of tumor vascular endothelial cells. Furthermore, while the specification discloses in vitro affects of second therapeutic agents such as hydrogen peroxide, thrombin and calcium flux agents,

the specification appears to be silent on the in vivo affects of administration of these second therapeutic agents.

While the presence of only one working example should never be the sole reason for rejecting claims as being broader than the enabling disclosure, one must evaluate all the facts and evidence and state why one would not expect to be able to extrapolate that one example across the entire scope of the claims. In the instant case, those of skill in the art would recognize the unpredictability that any/and or all antibodies that binds to any and/or all aminophospholipids on the luminal surface of blood vessels of a vascularized tumor could be used for the treatment of a vascularized tumor. With regards to antibody treatment, Jain (Scientific American July 1994) discloses barriers to the delivery of drugs into solid tumors. These impediments include (1) Non-uniform blood delivery to all areas of the tumor in which some areas of the tumor receive therapeutic agents and other areas of the tumor receive no therapeutic agent at all. (Page 60 col. 3); (2) Increased viscosity of blood in the tumor itself which also hinders drug delivery to the tumor (see paragraph bridging pages 60 and 61); (3) High liquid pressures in the interstitial matrix can retard the delivery of large therapeutic agents, such as antibodies, into tumors (page 61, Col. 1 paragraph 1); (4) Convection is a necessary mechanism by which larger therapeutics molecules such as antibodies, reach target cells which are not directly fed by the vasculature. Convection is not observed in large tumors (defined as more than ½ centimeter in diameter, page 62 col. 1) and convection is necessary for adequate drug delivery of molecules having a molecular weight of more than 5000 (page 61, col. 1 through page 63, col. 3) and (4) Molecules as large as antibodies (i.e., MW=150,000) would require several months to reach a uniform concentration in a tumor that measures 1 centimeter in radius (page 63, col. 2). Further, in the late 80's, Dillman (Annals of Internal Medicine, Volume 111, pages 592-603, 1989) summarized (see abstract) the status of in-vivo use of monoclonal antibodies for treating cancer wherein despite advances in biotechnology, many major hurdles persist including tumor cell heterogeneity, lack of cytotoxicity, and the development of human anti-mouse antibodies (HAMA). More recently, Weiner (Seminars Oncology, Vol. 26, No.4, 1999, pages 41-50) provided an overview of monoclonal antibody of therapy including some promising activity, however major obstacles to clinical efficacy still exist extending the unpredictability of this treatment. This includes impaired distribution and delivery of antibody to the tumor site, inadequate trafficking of potential cellular effectors to tumor, antigenic heterogeneity,

shed or internalized targets, insufficient target specificity, and induction of HAMA (page 43). Moreover, the exposure of any and/or all aminophopholipids on the luminal surface of a blood vessel of a vascularized tumor is unpredictable. For example, Ran et al. (Cancer Research 2002; 62: 6132-6140) disclose increased exposure of anionic phospholipids on the surface of tumor vessels. Specifically, Ran et al. teaches that the main anionic phospholipid that is localized by 9D2 and annexin V on tumor vasculature is likely to be PS due to it being the most abundant anionic phospholipids and its exposure on the cell surface is known to be regulated by environmental influences and injury (page 6139, 1st column, 1st full paragraph). Ran et al further teaches that other anionic phospholipids such as PI, PA and PG can not be excluded from also being exposed, but cautions this prediction based on these anionic phospholipids being less abundant and their membrane position not being as tightly regulated by environmental conditions (page 6139, 1st column, 1st full paragraph).

With regards to the in vitro vs. in vivo, those of skill in the art recognize that *in vitro* assays and or cell-cultured based assays are generally useful to observe basic physiological and cellular phenomenon such as screening the effects of potential drugs. However, clinical correlations are generally lacking. The greatly increased complexity of the *in vivo* environment as compared to the very narrowly defined and controlled conditions of an *in- vitro* assay does not permit a single extrapolation of *in vitro* assays to human diagnostic efficacy with any reasonable degree of predictability. *In vitro* assays cannot easily assess cell-cell interactions that may be important in a particular pathological state. Furthermore it is well known in the art that cultured cells, over a period time, lose phenotypic characteristics associated with their normal counterpart cell type. Freshney (Culture of Animal Cells, A Manual of Basic Technique, Alan R. Liss, Inc., 1983, New York, p4) teach that it is recognized in the art that there are many differences between cultured cells and their counterparts *in vivo*. These differences stem from the dissociation of cells from a three-dimensional geometry and their propagation on a two-dimensional substrate. Specific cell interactions characteristic of histology of the tissue are lost. The culture environment lacks the input of the nervous and endocrine systems involved in homeostatic regulation *in vivo*. Without this control, cellular metabolism may be more constant *in vitro* but may not be truly representative of the tissue from which the cells were derived. This has often led to tissue culture being regarded in a rather skeptical light (p. 4, see Major Differences In Vitro). Further, Dermer (Bio/Technology, 1994,

12:320) teaches that, petri dish cancer" is a poor representation of malignancy, with characteristics profoundly different from the human disease. Dermer teaches that when a normal or malignant body cell adapts to immortal life in culture, it takes an evolutionary type step that enables the new line to thrive in its artificial environment. This step transforms a cell from one that is stable and differentiated to one that is not. Yet normal or malignant cells *in vivo* are not like that. The reference states that evidence of the contradictions between life on the bottom of a lab dish and in the body has been in the scientific literature for more than 30 years. Clearly it is well known in the art that cells in culture exhibit characteristics different from those *in vivo* and cannot duplicate the complex conditions of the *in vivo* environment involved in host-tumor and cell-cell interactions. Furthermore, if the second therapeutic agent were hydrogen peroxide, those of skill in the art would recognize the unpredictability of administering hydrogen peroxide for the treatment of cancer. For example, Jordan et al. (J. Emergency Nursing 1991; 17: 8-10) discloses caveats of using hydrogen peroxide for the treatment of cancer. Specifically, Jordan found that the administration of hydrogen peroxide into closed spaces or body cavities results in hemolysis and damage to the erythocytic membrane leading to cellular lysis because the oxygen which is released has no free egress (page 9, 1st paragraph bridging 1st column and 2nd column). Moreover, Jordan et al. (page 10, 2nd column) concludes that one of the most recent unproven methods of cancer treatment that have been shown to cause life-threatening complications is IV injection of hydrogen peroxide. More recently, Symons et al (Medical Hypotheses 2001; 57: 56-58) discloses the use of hydrogen peroxide as a potent cytotoxic agent which is effective in causing cellular damage and which may be used in the possible treatment for certain tumors. Specifically, Symons et al. teach (page 57, 1st column, 3rd paragraph) that preliminary studies using tumour cells in vitro would suggest that hydrogen peroxide could mediate a rapid toxic effect. However, Symons et al. (page 57, 1st column, 3rd paragraph) cautions that the adaptation of this finding to in vitro therapy would require the development of systems/devices to deliver hydrogen peroxide to tumour tissues.

In view of the teachings above, and the lack of guidance and or exemplification in the specification, it would not be predictable that the method would function as contemplated. Thus, it would require undue experimentation by one of skill in the art to practice the invention as claimed.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

Claim 4, 6-7, 49-54, 57-58, 61-68 and 76-82 are rejected under 35 U.S.C. 103(a) as being unpatentable over Fishman et al (International Journal of Oncology, 10, 901-904, May, 1997) of record in further view of Hudziak *et al.* (U.S. 5,725,856, 1998) or record or Hillman et al. (Cell Immunol. 1995; 160: 257-263).

Fishman *et al.* teaches the use of purified IgG anti- phosphatydilserine (*anti-PS*) antibodies as an effective treatment for melanoma (abstract). Fishman further teaches that the anti-PS antibodies exerted an inhibitory effect of 76% on the development of lung metastatic foci in mice inoculated with B-16 melanoma cells (page 903, 1st column, 2nd paragraph).

Fishman *et al.* does not teach administration of anti-phosphatydilserine (anti-PS) antibodies in combination with a chemotherapeutic. Nor does Fishman disclose when the individual agents are administered.

Hudziak *et al.* teach a method of inhibiting growth of tumor cells which over express a growth factor receptor by administering antibodies either alone or in combination with other cytotoxic factors (abstract). Specifically, the patent teaches (column 6, lines 56-65) that a cytotoxic factor exerts a cytostatic (cell growth suppressive) and cytotoxic (cell destructive) effect and include, but are not limited to, chemotherapeutic drugs such as 5 fluorouracil, actinomycin D, doxorubicin and vinblastine or anti-angiogenic agents such as TNF-α.

Hillman et al. teach the administration of IL-4 to tumor bearing mice. Specifically, the reference discloses that IL-4 treatment reduced the number of lung metastases (abstract).

It would have been *prima facie* obvious to one of ordinary skill in the art at the time the invention was made to combine the teachings of the references so as to treat a vascularized tumor, e.g. cancer. One would have been motivated to do so because each of the therapeutics have been individually taught in the prior art to be successful at treating cancer. The instant situation is

amenable to the type of analysis set forth in In re Kerkhoven,205 USPQ 1069 (CCPA 1980) wherein the court held that it is prima facie obvious to combine two compositions each of which is taught by the prior art to be useful for the same purpose in order to for a third composition that is to be used for the very same purpose since the idea of combining them flows logically from their having been individually taught in the prior art. Applying the same logic to the instant claims, one of ordinary skill in the art would have reasonable expectation the by using an anti-PS antibody in combination with either a chemotherapeutic drug or an anti-angiogenic drug, one would achieve a method of treating a vascularized tumor.

Furthermore, it would have been prima facie obvious to one or ordinary skill in the art at the time the invention was made to optimize the administration times of the antibody and second therapeutic agent. One would have been motivated to do so because the selection of any order of performing process steps is *prima facie* obvious in the absence of new or unexpected results, see In re Burhans, 154 F.2d 690, 69 USPQ 330 (CCPA 1946) or In re Gibson, 39 F.2d 975. Thus, one would have a reasonable expectation that the administration of the antibody simultaneously, sequentially or prior to the administration of the second therapeutic agent would result in the treatment of a vascularized tumor.

Claim 4, 6-7, 49-54, 57-58, 61-68 and 76-83 are rejected under 35 U.S.C. 103(a) as being unpatentable over Fishman et al (International Journal of Oncology, 10, 901-904, May, 1997) and Hudziak *et al.* (U.S. 5,725,856, 1998) or Hillman et al. (Cell Immunol. 1995; 160: 257-263) in further view of Campbell, A.M. (Monoclonal Antibody Technology, Elsevier Science, NY, 1986, pages 1-33).

The combination of Fishman et al. and either Hudziak et al. or Hillman et al, as taught above, teach a method of treating a vascularized tumor comprising administering an antibody which binds to phosphatidylserine in combination with a second therapeutic agent.

The combination of Fishman et al. in view of either Hudziak et al. or Hillman et al. does not teach that the antibody is a monoclonal antibody.

Campbell et al. teach a comparison of monoclonal antibodies and conventional antiserum (page 4, 1.2). Specifically, the reference teaches that a specific advantage of monoclonal antibodies is

their specificity, which can be used in tumor immunotherapy, wherein the antibody may be used by used by itself, or coupled to drugs or toxins (page 7, 2nd column 1st full paragraph).

It would have been *prima facie* obvious to one of ordinary skill in the art at the time the invention was made to generate a monoclonal antibody to phosphatidylserine in view of the teachings of Campbell et al.. One would have been motivated to do so because as taught by Campbell et al., monoclonal antibodies have a higher specificity than conventional anti-serum antibodies. Thus, one of ordinary skill in the art would have a reasonable expectation that by generating a monoclonal antibody to phosphatidylserine as taught by Fishman et al, one would have method of reducing tumor growth with an antibody that has a higher specificity to phosphatidylserine than the antibody previously used.

Claim 4, 6-7, 9, 49-54, 57-58, 61-68, 71 and 76-82 are rejected under 35 U.S.C. 103(a) as being unpatentable over Fishman et al (International Journal of Oncology, 10, 901-904, May, 1997) and Hudziak *et al.* (U.S. 5,725,856, 1998) or Hillman et al. (Cell Immunol. 1995; 160: 257-263) in further view of Devaux et al (U.S. Patent 6,824,780 B1, 10/29/1999).

The combination of Fishman et al. in view of either Hudziak et al. or Hillman et al, as taught above, teach a method of treating a vascularized tumor comprising administering an antibody which binds to phosphatidylserine in combination with a second therapeutic agent.

The combination of Fishman et al. in view of either Hudziak et al. or Hillman et al. does not teach that the antibody is a humanized antibody.

Devaux et al also discloses the generation of humanized antibodies. Specifically, Devaux et al. teach that humanized antibodies are better suited for human therapy because they reduce immunogenicity and human anti-mouse antibody (HAMA) response (see columns 23-24).

It would have been *prima facie* obvious to one of ordinary skill in the art at the time the invention was made to generate a humanized antibody to phosphatidylserine in view of the teachings of Devaux et al. One would have been motivated to do so because as taught by Devaux et al., humanized antibodies are better suited for human therapy because they reduce immunogenicity and human anti-mouse antibody (HAMA) response. Thus, one of ordinary skill in the art would have a reasonable expectation that by generating a humanized antibody to phosphatidylserine as

taught by Fishman et al, one would have an effective antibody treatment of vascularized tumors in a human patient which would not generate a HAMA response.

Claim 4, 6-8, 49-54, 57-58, 61-68, 70 and 76-83 are rejected under 35 U.S.C. 103(a) as being unpatentable over Fishman et al (International Journal of Oncology, 10, 901-904, May, 1997) and Hudziak *et al.* (U.S. 5,725,856, 1998) or Hillman et al. (Cell Immunol. 1995; 160: 257-263) in further view of Nicolotti (US 4,837,003, 1989).

The combination of Fishman et al. and either Hudziak et al. or Hillman et al, as taught above, teach a method of treating a vascularized tumor comprising administering an antibody which binds to phosphatidylserine in combination with a second therapeutic agent.

The combination of Fishman et al. in view of either Hudziak et al. or Hillman et al. does not teach that the antigen binding fragment of an antibody is an Fab fragment.

Nicolotti teaches antibody fragments, rather than whole antibodies, are better-suited fro in vivo use for diagnositic and therapeutic applications because they are better able to penetrate the desired target site, as well as minimize the problems of immunogenicity and cross-reactivity associated with whole antibodies (column 1, lines 43-49).

It would have been *prima facie* obvious to one of ordinary skill in the art at the time the invention was made to generate a antibody fragments to phosphatidylserine in view of the teachings of Nicolotti. One would have been motivated to do so because as taught by Nicolotti, antibody fragments when used in vivo reduce immunogenicty and cross-reactivity. Thus, one of ordinary skill in the art would have a reasonable expectation that by generating antibody fragments to phosphatidylserine, one would have an antibody fragment which binds to phosphatidylserine which does not cross react and minimizes the problems of immunogenictiy associated with whole antibodies.

Note: The Fishman et al. reference was used in a prior Non-Final Office action (9/08/2004) for the rejection of claims 4, 6-7, 49-50 and 68 under 35 U.S.C. 103(a) as being unpatentable over Fishman et al (International Journal of Oncology, 10, 901-904, May, 1997) in further view of Tschmelitsch et al. (Cancer Research 57, 2181-2186, June 1, 1997). After reviewing

Applicants' amendments the rejection was withdrawn without an explanation and/or reply to Applicants remarks.

Because the Fishman reference is being applied again, the Examiner would like to take a moment to respond to Applicants arguments (12/12/2004) pertaining only to Fishman in order to expedite prosecution. The reason why the Examiner will only address Fishman and not Tschmelitsh et al and/or Hudziac et al. whom disclose chemotherapeutics is because the court has held that it is prima facie obvious to combine two compositions each of which is taught by the prior art to be useful for the same purpose in order to for a third composition that is to be used for the very same purpose since the idea of combining them flows logically from their having been individually taught in the prior art see In re Kerkhoven,205 USPQ 1069 (CCPA 1980).

In reference to the Non-Final Office Action (09/08/2004) which held that Fishman et al., as discussed above, discloses the use of purified IgG anti- phosphatydilserine (*anti-PS*) antibodies as an effective treatment for melanoma (abstract), wherein the administration of the anti-PS antibodies exerted an inhibitory effect of 76% on the development of lung metastatic foci in mice inoculated with B-16 melanoma cells (page 903, 1st column, 2nd paragraph), Applicants (page 31, 12/12/2004) primarily argue that the Action and Fishman omits two main limitations, e.g., "vascularized tumor" and "binds to an aminophospholipid on the luminal surface of blood vessels of the vascularized tumor" and insist that the proper interpretation of the claims should be as drawn to targeting aminophospholipids on the luminal surface of blood vessels of the vascularized tumor. (emphasis added).

In response to this argument, a careful review of the pending claims does not appear to recite the limitation "targeting"; and any argument pertaining to this "claim interpretation" has not been considered because the currently pending claims are drawn to a method of **treating** and not targeting a vascularized tumor comprising administering an antibody that binds to an aminophospholipid on the luminal surface of blood vessels of the vascularized tumor. While the Examiner concedes that Fishman does not explicitly characterize the resulting tumor as a vascularized tumor, Applicants have not provided evidence or a patentable difference between the claimed method of treating a vascularized tumor with an antibody that binds to an aminophospholipid on the luminal surface of blood vessels of the vascularized tumor and inhibiting the development of metastatic foci in mice inoculated with B-16 melanoma cells with an antibody

that binds to phosphatidylserine. For example, the specification (page 11, lines 1-7) teaches that the term "vascularized tumor" most preferably means a vascularized, malignant tumor, solid tumor or "cancer". Therefore, in view of the specification, it appears that Fishman has met the limitation of a vascularized tumor with the recitation of "cancer" (see page 903, 1st column). Moreover it appears that Fishman's inoculation of a mouse with B-16 melanoma cells may result in the formation of a vasularized tumor. For example, Holash et al (Oncogene 1999; 18: 5356-5362), disclose a modification of the prevailing view that most malignancies and metastases originate as avascular masses that only belatedly induce angiogenic support, wherein the modification is that instead of growing avascularly, many tumors rapidly co-opt existing host vessels to form an initially well-vascularized tumor mass (page 5360, 1st column, Conclusion and Discussion). Specifically, Holash disclose that this effect is not only observed in rats inoculated with gliomal cells, but extends to other tumors (page 5360, 1st column, Findings in gliomas are true for other tumors). As such, the "vascularized" limitation does not appear to differ the currently pending claims from the tumor of the prior art. Furthermore, the Examiner concedes that Fishman et al. does not explicitly teach that the antibody binds to an aminophosholipid on the luminal surface of blood vessels of the vascularized tumor and agrees with Applicants assertion that Fishman teaches that phosphatidylserine is expressed on the outer membrane of tumor cells and the inner leaflet of normal cells. However, the Examiner does not agree that Fishman explicitly omits the limitation "binds to an aminophospholipid on the luminal surface of blood vessels of the vascularized tumor". For example, the specification teaches that aminophospholipids of the invention include phosphatidylserine. Specifically, the specification discloses that phosphatydilserine is expressed in tumor blood vessels (Examples VIII page 163). Thus, in view of the specification, there does not appear to be any difference between the antibody/aminophospholipid in the presently claimed invention and that of the prior art. Moreover, there does not appear to be a patentable difference between the active steps involved in the currently pending claims and those taught by Fishman, ie. administering an antibody that binds to an aminophospholipid, specifically phosphatidylserine. Nor does there appear to any difference in the end result, e.g. treatment of a vascularized tumor. Absent evidence, what is to say that the antibody of Fishman et al. will not bind to phosphatidylserine which is expressed on the luminal surface of blood vessels on the vascularized tumor, wherein the tumor expresses phosphatidylserine on the outer surface? The office does not have the facilities and

resources to provide the factual evidence needed in order to establish that the product of the prior art does not possess the same material, structural and functional characteristics of the claimed product. In the absence of evidence to the contrary, the burden is on the applicant to prove that the claimed product is different from those taught by the prior art and to establish patentable differences. See In re Best 562F.2d 1252, 195 USPQ 430 (CCPA 1977) and Ex parte Gray 10 USPQ 2d 1922 (PTO Bd. Pat. App. & Int. 1989).

Therefore, NO claim is found allowable.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Brandon J. Fetterolf, PhD whose telephone number is (571)-272-2919. The examiner can normally be reached on Monday through Friday from 8:30 to 5:00.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Jeff Siew can be reached on 571-272-0787. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

Brandon J Fetterolf, PhD
Examiner
Art Unit 1642

BF

JEFFREY SIEW
SUPERVISORY PATENT EXAMINER
10/17/05